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Newcastle disease - A special review of immunosuppression

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I. – Introduction

Newcastle disease (ND) has remained almost the only classical viral poultry infection that resists all efforts for its eradication. Since its first incidence and description, the approach to its control has been changed only slightly, so the two main fields in that sense have remained unchanged : specific and non-specific control of the disease.

II. – The specific control of Newcastle disease

1. Vaccines

Attenuated, mesogenic and lentogenic strains have been applied to control ND. Mesogenic, like Haifa (Komarov), Mukteswar, H. (Hertsfordshire) or Roakin MK 107 (L) have good immunogenic abilities. Applied individually, they provide specific immunity until the end of their productive life of one year or more. Unfortunately it is impossible to use them at a rate sufficient to prevent the spreading of ND. Moreover, perentheral application is a way to spread the disease from hosts to healthy poultry. Mesogenic vaccines are not used in countries with highly developed poultry production ; in Mediterranean countries they are almost completely replaced by lentogenic vaccinal strains that are easy to use in large poultry agglomerations through mass applications. Satisfactory immunity can be achieved by spraying lentogenic strains of ND vaccine in practically 60 hours after vaccination. There is no faster way of inducing the refractibility of an organism to the infection, except through passive immunisation by immune serum, but this is definitely unacceptable for everyday practice.

For the application of lentogenic vaccine in drinking water, far stronger doses of the virus are needed and the immunity is obtained much later (after seven or eight days) and various mistakes are possible. For these reasons the vaccination is often unsucessful with a so-called "break of immunity". That is why in Croatia eyedrop vaccination or vaccine spraying is allowed, but its application in drinking water is forbidden.

Current vaccination programmes against ND using the exclusive application of live viral vaccines differ from country to country and very often between regions, or even between production organizations. There are no legislative norms by which the application of these vaccines could be defined, which is perfectly understandable because the analyses of the disease are still incomplete and the possibilities of its control are still insufficiently investigated.

In recent application programmes, mesogenic and lentogenic ND vaccines have been combined, showing positive results in controlling the disease outbreaks.

Inactivated oil vaccines in any form, are acceptable in all countries regardless of the possible legal orders against the intake of "live" ND antigene, even lentogenic ones. The inactivated oil vaccine is, by definition, a specimen made of the whole viral corpuscle or only from nucleic acid.

There are some undeniable advantages of inactivated vaccines in relation to the live ones. First of all, by using these vaccines the disease cannot be spread and the undesirable mutation of antigene is not possible. They are applied before complete sexual maturity of the poultry and because of their longlasting immunity, they last until the end of the productive use of the poultry regardless of their category. The most significant advantage of these vaccines is the high immunity rate they induce.

Disregarding the sort of the vaccines applied or the vaccination programme, the resistance of vaccinated poultry to pathogenic viruses can result not only in avoiding the disease or even death, but also in reducing production abilities, egg drop or growth depression that, in the organism of vaccinated poultry, can be caused by pathogenic virus.

All vaccinal and many other strains of ND virus induce the production of specific HI antibodies in poultry. Their quality is in a significant positive correlation with the immunity rate of poultry, so it is possible to ascertain the specific immunity of vaccinated poultry by relatively simple laboratory trials. The relation between the findings of specific HI antibodies in the serum and the possible results of the infection with pathogenic ND virus is shown in **Table 1** (according to Allan *et al.*, 1978).

2. Variability of the immune response

The immune reaction of very young poultry is much poorer than that of matured poultry or that several weeks old. Unfortunately, the ND virus infects very young animals too, so protection is needed even then.

There are differences between particular genetic lines and their hybrids in the immune response ability. It seems that these differences are related to the general resistance to micro-organisms and only in a minor way to the specific agent. The morphological basis of the resistance of an animal includes immunocompetent organs or a complete immune system. The differences between particular hybrids or poultry lines can already be noticed by simple weighing the *bursa* of *Fabricius*. Diseases like Marek's disease or lymphoid leucosis are significant indicators not only of the specific resistance, but also of the resistance to all possible noxious elements in the environment.

A. Effect of viruses

The immune system of poultry can be destroyed by different viruses. Among them, two are prominent : the viruses of Marek's and Gumboro diseases. In Yugoslavia we had the opportunity to follow the incidence of Gumboro disease during 11 years and the correlating immune response of broilers singly and after twofold vaccinations against ND with the vaccine prepared from La Sota strains of local origin. The results are shown in **Table 2** and **Graph 1** (according to Bidin, 1980).

In 1972 the high incidence of Gumboro disease in Yugoslavia was followed by the drop in the immune response to a specific vaccine (Mazija *et al.*, 1984). The introduction of twofold vaccination at the age of 4 or 25 days by spraying has highly improved the immune response of chickens, but it still remains that in case of infection with pathogenic virus, this technique cannot completely prevent mortality. In 1977 the mass vaccination against Gumboro disease began and in 1978 it was completed. The immune response of chickens, even after the first vaccination against ND at the age of 4 days, achieved the values expressed by HI titre identical to those before the outbreak of Gumboro disease. After repeated vaccination, the HI titre was doubled (1:66,67).

There are many examples of immunosuppressive effects of Marek's disease virus. This infection complicates the clinical picture and the course of coccidiosis (Biggs *et al.*, 1968). The discovery that B cells of all three immunocompetent organs – tymus, spleen and *bursa* of *Fabricius* are acceptable to early

cytolitic infection with the virus of Marek's disease (Shek *et al.*, 1983) completely explains the fact mentioned. This is especially so considering the fact that in the continuation process, the degeneration even of T cells of the same organs shows up. The pathogenic virus of Marek's disease reduces, by its activity, the common resistance to diseases even before causing the clinical signs of the disease. These unconvenient effects could be recognised most clearly in the comparative investigations of production abilities of chickens of the control group and the experimental group vaccinated with Marek's disease vaccine. The results of such experiments are shown in **Table 3.**

Immediately after being hatched, day-old chicks were vaccinated with 1,000 PFU HVT per chick suspended in 0.4 ml of diluent. Significant differences between vaccinated and unvaccinated chicks have shown up, especially in final body weight and feed conversion and, to a lesser extent, mortality.

Immunosuppressive effects can also be provoked by other viruses and different micro-organisms, including oncogenic RNA viruses and adenoviruses. Very often several micro-organisms act simultaneously, resulting in the multicausal basis of most diseases that cause poultry mortality in all production and age categories.

B. Effect of environment and nutrition

Environment and various nutrients also have a significant influence on the immune system of poultry. They act directly, like drugs, toxins and contaminants or indirectly, like heat, cold, overpopulation, injuries and vaccination procedures, etc... (Fahey, 1983).

For example, the shortage of valine (it makes 7% of poultry gammaglobuline) reduces the HI titre (Bhargava *et al.*, 1970). The total amount of proteins in feed and the quantity of lysine, methionin or methionin + cystin in feed (Mazija *et al.*, 1981) all have significant effects on the immune response to ND vaccine.

Vitamins, like vitamin A (Leutskaya and Fais, 1977), B complex (Panda and Combs, 1963) and particularly vitamin E (Law and Nockels, 1976) have been identified as substances significantly affecting the immune response to ND vaccine.

Concerning metals, the important one is iron. The addition of 82 mg/kg of feed significantly improves the HI immune response to La Sota vaccine (Serman *et al.*, 1980). Selenium, similar to zinc, stimulates antibody production (Spallholz *et al.*, 1973 ; Burns, 1983). Copper added at the amount of 400 mg/kg of feed increases the survival rate of chicks after infection with *S. gallinarum* (Hill *et al.*, 1977).

Special attention has been paid to the investigation of the mechanism of the role of zinc and selenium in the development of immunocompetency. With regard to this, attention has also been paid to the relation between vitamin A and zinc, because it has been proved that a shortage of vitamin A decreases the rate of zinc resorption from chick crop. The immune system of chicks is affected in some way by almost all mycotoxins. Besides mortality, specially in extraordinary sensible turkeys, it has been shown that it increases the susceptibility of chicks to salmonella (Boonchuvit and Hamilton, 1975), pasteurella, erysipela, coccidias and fungi (Chevill, 1979) at the rate that depends on the dose of the mycotoxin.

The quantity of 2.5 ppm of aflatoxin reduces the motility and phagocytic activity of monocytes (Chang and Hamilton, 1979). The effect of aflatoxin on the production of antibodies varies a lot, probably reflecting the depressive effect of aflatoxin on the activity of complements and the opsonisation and phagocytosis. The above mentioned aflatoxin quantity (2.5 ppm) in chicken feed at the age of 0-28 days significantly increases mortality but not the immune response to ND vaccines of infectious bronchitis (Giambrone *et al.*, 1978). Recent investigations (Boulton *et al.*, 1982) have proved that a quantity as low as 0.5 ppm of aflatoxin in poultry feed during three months decreases the immune response after single but not multiple vaccination againts ND. A considerably higher dose, 200 mg of aflatoxin given daily during three weeks, reduces the production of antibodies in chicks infected by pathogenic ND vis (Mohiddin *et al.*, 1981).

Ochratoxin A provokes strong lymphocytopenia in chicks and at a smaller rate monocytopenia if it happens to be in feed in quantities as low as 0.5-800 ppm during three weeks (Chang *et al.*, 1979). Considerably lower doses of the mycotoxin mentioned (1.4 ppm or less) provoke reversible destruction of lymphocytes in the follicles of *bursa* of *Fabricius* (WU Ni, 1982). The active or passive immunity against ND and infectious bronchitis, respectively, are affected suppressively by the same quantities (Mazija *et al.*, 1982).

Few data concerning specific effects of different drugs immune response against ND are available. Such substances are, for instance, sulphadimetoxine or ormetoprim. After applying the live vaccines, both inhibit the immunity response (Derieux, 1977). Polychlorinated biphenols (PCP's) at the dose of 20 ppm reduce the hatchability and chick growth rate (Ringer and Polin, 1977) and also the weight of *bursa* of *Fabricius* (Harris *et al.*, 1976). The direct effect of various pesticides on the immune response of chickens to ND has not been investigated completely. Nevertheless, it is known that polycyclic organochlorides in the amount of 100 ppm decrease the concentration of IgG in chicken blood serum (Subba Rao and Glick, 1977) ; in 1976 its further use was forbidden in the USA.

The toxic effect of TMTD (Tetrametiltiuram disulfid) on chicks (Ramljak *et al.*, 1986) is manifested by inducing the specific clinical signs. Preliminary investigations of TMTD effects on HI ND antibodies already obtained, indicate their fast excretion even at a contamination level as low as 5 ppm for several days.

The mechanism of this appearance has not been investigated yet (Mazija *et al.*, in press).

Indirectly, all the stimuli that provoke the clinical syndrome described by the name STRESS, influence the immune system of chickens. In other words, all the stimuli that provoke the glucocorticosteroid secretion in adrenal gland adversely influence the immune system of poultry (and other animals). Temperature, relative air humidity, thirst, overpopulation and social stress of the poultry removed from one pen to another, are included in this (Fahey, 1983). After a treatment seeming to be quite trivial, like feed replacement (starter with finisher), vaccination against ND will have no adverse effect on broiler weight but the effect on HI specific antibody titre will be significantly (11,57:119,43) adverse in the period of 14 days after vaccination against ND (Findrik *et al.*, 1980).

III. – The non specific control of Newcastle disease

Included here are only the technological principles that prevent the spread of Newcastle disease and almost all other poultry diseases. These principles are : all in - all out, one age on a farm, one production purpose, one genetic basis and a long-enough pause between cycles so a radical break in transmitting biological contamination from the processing cycle of previous poultry generation is possible.

The procedures which prevent the spreading of ND are also non-specific but their purpose is to control the disease. They were described by Hanson (1984) who ranked the possibilities by which ND spreads according to their importance. They are shown in **Table 4.**

It is obvious that in planning for ND control, particular measures should be taken. The poultry experts, working either in the immediate production or in research institutions are not able to cope with the measures required only by themselves. It would be useful to evoke the essential premises that should be the basis for ND control in Yugoslavia (Mazija *et al.*, 1985), measures that almost certainly could be applied in all Mediterranean countries:

1°– The whole country should be treated as an epizootiologically uniform area.

2°– According to the Animal Protection from Infectious Diseases Act, Newcastle disease should be controlled rigorously, as well as other infectious diseases that endanger the whole country.

3°– Programmes for Newcastle disease control in a country must be uniform, with no excuse of any kind of individual feasibilities, local epizootiological conditions or economic interests.

4°– Concern for Newcastle disease control must become commonplace.

The uniformity of ND control in the whole country means that by uniform vaccination conducted on farms it is also possible to protect the individual poultry breedings against ND. This original treatment was successfully tested in Yugoslavia in 1981 and 1982 (Mazija and Medven, 1981 ; Medven and Mazija, 1982) and applied in practice in 1983 when ND broke out on a broiler farm where it had been brought from the diseased individual poultry breeding. The infected poultry has been removed, and in the endangered area of 44 villages, 8,632 households containing 331,418 hens and turkeys of all age categories have been vaccinated. On average, the smallest number of poultry in individual households ranged from at least 17.32 to mostly 59.08 animals. The "live" La Sota vaccine of Yugoslav origin has been applied by spraying. Through these measures, the further spreading of the disease was prevented. Moreover, in the next year, for which data are available, in the region where poultry of individual breeding were thus vaccinated, there was no outbreak of ND.

Most or all Mediterranean countries also have individual poultry breeding that is a permanent source of ND, that may infect poultry on larger farms.

The described procedure of specific poultry protection is one of the ways of improving the epizootiological situation. The selection of thermostabile strains of vaccinal ND viruses of good immunogenic abilities would make possible not only the application of live vaccine in small poultry operations by means of spraying more successfully, but also to mix it in the feed. According to many experts, this way of vaccination could be a large step forward in ND control.

Finally, it should be stated that all Mediterranean countries have the scientific knowledge to control ND. For that reason, taking all of them into account, they will be able to choose the simplest way to do so. All factors that could have immunosuppressive effects on poultry should be thoroughly reconsidered, certainly not just to ensure qualitative immunity against ND but, above all, to ensure better human health.

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Table 1: The relation between HI titre of serum and immunity to the challenge by pathogenic virus N.D. (1:)

HI titre	Mean value	Standard deviation	Consequences of challenge
$= 2^2$			100 % mortality
$2^2 - 2^5$	$2^{3,75}$	0.4	10 % mortality
$2^4 - 2^6$	$2^{5,2}$	0.35	0 % mortality
$2^6 - 2^8$	$2^{6,5}$	1.2	Heavy egg drop with no mortality HI titre of serum 2^{14}
$2^9 - 2^{11}$	$2^{10,3}$	1.4	No egg drop, no mortality, HI titre of serum from 2^{11} to 2^{12}
$2^{11} - 2^{13}$	$2^{11,2}$	1.3	The flock is perfectly protected from egg drop in the period of six months or more

Allan *et al.*, 1978.

Table 2: Average value of HI N.D. antibody titre in the serum of broilers after single and two fold vaccination (from 1968 to 1970)

Year	Total amount of sera analysed	HI titre after vaccination			
		I		II	
		Sera analysed	HI titre*	Sera analysed	HI titre*
1968	70	70	17.73	-	-
1969	120	120	7.47	-	-
1970	60	60	27.15	-	-
1971	110	110	25.31	-	-
1972	390	390	39.58	-	-
1973	160	40	29.88	120	53.30
1974	780	560	8.67	220	52.08
1975	2,270	1,220	9.69	1,050	18.29
1976	4,417	2,657	8.30	1,760	17.51
1977	3,606	2,696	8.66	910	22.63
1978	6,580	2,770	33.77	3,810	66.67

* The value of HI titre is defined as 1 :

Table 3: Body weight, feed consumption and mortality of chickens of the control and experimental group vaccinated against Marek's disease

Indicators of the success of chicken fattening	Experimental group*		Control group*	
	At the age of 42 days	At the age of 48 days	At the age of 42 days	At the age of 48 days
Average body weight (gr)	1,632	1,815	1,516	1,719
Weekly gain (gr)	504	183	429	203
Total feed consumption (gr)	2,872	3,747	3,117	3,908
Feed consumption (kg)	1,759	2,064	2,056	2,273
Mortality (%)	3.70	4.06	4.06	4.42
Productional number	212.80	174.80	168.40	150.60

* In each groups there were 5,000 chickens.

Source : Mazija *et al.*, 1983.

Table 4: Possible ways of spreading the Newcastle disease ranked according to their importance

1. Movements of clinically unapparent carriers.
2. Movements of staff from contaminated flocks to uninfected ones.
3. Movements of different vehicles from flock to flock.
4. Migration of mice that are (for seven days or more) the carriers of ND virus. During harmless removal of the flock and cleaning and desinfecting the pens, mice and wild birds looking for feed transmit ND virus to other poultry farms.
5. Mechanical propagation of ND virus by flies.

According to Hanson, 1984.

Graph 1 : HI N.D. antibody titre in chickens after vaccination (from 1968 to 1978)